The Glasgow Prognostic Score Before Curative Resection May Predict Postoperative Complications In Patients With Gastric Cancer

Yota Shimoda

Kanagawa Cancer Center: Kanagawa Kenritsu Gan Center

Hirohito Fujikawa

Kanagawa Cancer Center: Kanagawa Kenritsu Gan Center

Keisuke Komori

Kanagawa Cancer Center: Kanagawa Kenritsu Gan Center

Hayato Watanabe

Kanagawa Cancer Center: Kanagawa Kenritsu Gan Center

Kosuke Takahashi

Kanagawa Cancer Center: Kanagawa Kenritsu Gan Center

Kazuki Kano

Kanagawa Cancer Center: Kanagawa Kenritsu Gan Center

Takanobu Yamada

Kanagawa Cancer Center: Kanagawa Kenritsu Gan Center

Manabu Shiozawa

Kanagawa Cancer Center: Kanagawa Kenritsu Gan Center

Soichiro Morinaga

Kanagawa Cancer Center: Kanagawa Kenritsu Gan Center

Kenji Katsumata

Tokyo Medical University: Tokyo Ika Daigaku

Akihiko Tsuchida

Tokyo Medical University: Tokyo Ika Daigaku

Takashi Ogata

Kanagawa Cancer Center: Kanagawa Kenritsu Gan Center

Takashi Oshima (✉ ohshimatakashi@yahoo.co.jp)

Kanagawa Cancer Center: Kanagawa Kenritsu Gan Center <https://orcid.org/0000-0001-5818-8649>

Research Article

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Abstract

Purpose: Despite improvements in surgical techniques and devices and perioperative care of gastric cancer (GC), the rate of postoperative complications still has not decreased. If patients at high risk for postoperative complications could be identified early using biomarkers, these complications might be reduced. In this study, we investigated usefulness of the preoperative Glasgow Prognostic Score (GPS) as a predictive factor for complications after surgery in patients with stage II/III GC.

Methods: This study retrospectively analyzed the outcomes of 424 patients who underwent curative surgery for pathological Stage II/III GC from February 2007 to July 2019 at a single center. The GPS was assessed within 4 days before surgery. To identify independent risk factors for postoperative complications, univariate and multivariate analyses were performed using a Cox proportional hazards model.

Results: The numbers of patients with a GPS of 0, 1, and 2 were 357, 55, and 12, respectively. The rate of complications after surgery was significantly higher among patients with a GPS of 1 or 2 than among patients with a GPS of 0 ($p = 0.008$). Multivariate analysis identified a GPS of 1 or 2 as an independent predictive factor for postoperative complications ($p = 0.037$).

Conclusion: The preoperative GPS may be a useful predictive factor for postoperative complications in patients with stage II/III GC. Being aware of the risk of complications after surgery as indicated by the GPS before surgery may promote safe and minimally invasive surgery that we expect will improve outcomes in these patients.

Introduction

Gastric cancer (GC) is the fifth most prevalent carcinoma in the world, with 1,089,103 new cases in 2020, and the fourth leading cause of death from cancer, with 768,793 deaths globally [1]. The standard treatment for pathological (p)Stage II/III GC is curative surgery and adjuvant chemotherapy [2]. Despite improvements in surgical techniques and devices and perioperative care, the rate of postoperative complications still has not decreased. Recent studies reported postoperative complication rates after GC resection of 17.4–24.5% [3–5]. Postoperative complications may significantly impact both long-term and short-term outcomes because they can sometimes lead to the production of cytokines that are growth factors for GC micrometastases. Complications prolong hospital stays, reduce the quality of life of patients, and increase health care costs [6, 7]. Additionally, postoperative complications often delay the initiation of adjuvant chemotherapy and decrease patients' tolerance of chemotherapy [8]. Furthermore, a postoperative systemic inflammatory response is related to poor cancer-specific survival, independent of the tumor stage [9]. Postoperative complications contribute to poor cancer-specific survival in various types of cancer, including GC [10–12]. Therefore, if patients at high risk for postoperative complications could be identified early using biomarkers, these complications might be reduced by selecting risk-

adapted procedures and perioperative measures. Such biomarkers must be easy-to-use, low-cost, rapid, objective measures accessible to all patients and hospitals.

The Glasgow Prognostic Score (GPS) has been reported as a parameter that elevated serum C-reactive protein (CRP) levels reflects a progression cancer stage and decreased serum albumin levels reflects an indicator of malnutrition [13–18]. Therefore, we hypothesized that the GPS might be a useful predictor of postoperative complications. In this study, we investigated the usefulness of the GPS before surgery in predicting complications after surgery in patients with stage II/III GC.

Patients And Methods

Patients

The study was approved by the Research Ethics Committee of the Kanagawa Cancer Centre in Yokohama, Japan before the study started (approval number: Epidemiological Study, 2019 – 113). A total of 623 consecutive patients who underwent gastrectomy with D2 lymph node dissection for pStage II/III GC from February 2007 to July 2019 at the Kanagawa Cancer Centre and measured serum albumin and CRP levels before surgery documented in their medical record were eligible for this study. Patients were excluded if any of the following criteria applied: (1) preoperative treatment including neoadjuvant chemotherapy, (2) remnant GC, (3) stage IV disease, and (4) non-curative (R1 or R2) resection.

Definition of GPS

The GPS was calculated using the serum CRP and serum albumin levels extracted from the medical records. Serum albumin and CRP levels before surgery were assessed within 4 days before surgery. The GPS was scored by allocating one point each for hypoalbuminemia (< 3.5 mg/dL) and elevated CRP (> 1.0 mg/dL). Patients with a hypoalbuminemia (< 3.5 mg/dL) and elevated CRP (> 1.0 mg/dL) were assigned a score of 2. Those with a hypoalbuminemia alone or elevated CRP alone were assigned a score of 1. Those with normal albumin levels (≥ 3.5 mg/dL) and CRP ($\text{CRP} \leq 1.0$ mg/dL) and were assigned a score of 0 [19].

Surgical procedure and perioperative care

Patient with cStage IB disease underwent laparoscopy-assisted gastrectomy with D1 + lymphadenectomy, and those with cStage II/III disease underwent open gastrectomy with D2 lymphadenectomy according to the TNM classification (8th edition).

Our center uses the “enhanced recovery after surgery” protocol, which has been described in a previous study [20]. Oral intake was initiated on postoperative day (POD) 1, beginning with water. Patients began to eat on POD 2, starting with rice gruel and advancing in three steps to regular food intake on POD 6.

Data collection

All variables, including patient age, sex, body mass index (kg/m^2), type of surgery, operative time, blood loss, depth of invasion, and lymph node metastasis, were collected from the clinicopathological database

in Kanagawa Cancer Centre. All resected specimens had been examined and histopathologically staged according to UICC TNM 8th edition [21]. Complications after surgery were defined as those observed within 1 month after surgery that were grade 2 or higher according to the Clavien-Dindo classification [22].

Evaluations and statistical analysis

Patients were divided into a GPS 0 group and a GPS 1 or 2 group based on their preoperative GPS. We used the Mann-Whitney U test for comparison of age, body mass index, operation time, intraoperative blood loss between two groups. Categorical variables were analyzed using Pearson's χ^2 test. To identify independent risk factors for postoperative complications, univariate and multivariate analyses were performed using a Cox proportional hazards model. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA). Statistical significance was defined at a p -value < 0.05 .

Results

Comparison of clinicopathological characteristics between the GPS 0 and GPS 1 and 2 groups

In this study, a total of 424 patients were examined. A flow diagram of the patient selection is shown in Fig. 1. The numbers of patients with a GPS of 0, 1, and 2 were 357, 55, and 12, respectively. The clinicopathological characteristics of the GPS 0 and GPS 1 and 2 groups are shown in Table 1. Age, operative time, blood loss during surgery, and pathological lymph node metastasis were significantly higher in the GPS 1 and 2 group than in the GPS 0 group. The body mass index was significantly lower in the GPS 1 and 2 group than in the GPS 0 group.

Table 1
Clinicopathological characteristics of patients in the GPS 0 and GPS 1 and 2 groups

GPS			
Variables/categories	0 (n = 357)	1 and 2 (n = 67)	p-value
Age, years (mean ± SD)	66.7 ± 11.0	72.2 ± 8.8	< 0.001
Sex, n (%)			
Male	239 (67)	43 (64)	0.66
Female	118 (33)	24 (36)	
Body mass index, kg/m² (mean ± SD)	22.7 ± 3.1	21.8 ± 3.1	0.035
Type of surgery, n (%)			
Distal gastrectomy	199 (56)	30 (45)	0.098
Total gastrectomy	158 (44)	37 (55)	
Operation time, min (mean ± SD)	214.6 ± 63.6	238.8 ± 71.5	0.005
Blood loss, mL (mean ± SD)	335.6 ± 334.9	497.4 ± 404.5	0.001
Pathological tumor depth, n (%)			
T2	98 (27)	12 (18)	0.157
T3	104 (29)	26 (39)	
T4	155 (44)	29 (43)	
Pathological lymph node metastasis, n (%)			
N0	135 (38)	14 (21)	0.038
N1	71 (20)	13 (19)	
N2	65 (18)	17 (25)	
N3	86 (24)	23 (34)	
GPS, Glasgow Prognostic Score; SD, standard deviation			

Comparison of postoperative complications between the GPS 0 and GPS 1 and 2 groups

Sixty-six postoperative complications (18%) were observed in the GPS 0 group and 22 (33%) in the GPS 1 and 2 group. The rate of postoperative complications was significantly higher in the GPS 1 and 2 group than in the GPS 0 group ($p = 0.008$). The postoperative complications in the two groups are shown in

Table 2. The rate of infectious complications, such as pancreatic fistula, anastomotic leakage, pneumonia, intra-abdominal abscess, and wound infection, was significantly higher in the GPS 1 and 2 group than in the GPS 0 group ($p = 0.008$).

Table 2
Comparison of postoperative complications between the GPS 0 and GPS 1 and 2 groups

Variables / categories, n (%)	GPS		p-value
	0 (n = 357)	1 and 2 (n = 67)	
All postoperative complications	66 (18)	22 (33)	0.008
Pancreatic fistula	21 (6)	6 (9)	0.345
Anastomotic leakage	12 (3)	4 (6)	0.304
Ileus	7 (2)	3 (4)	0.213
Pneumonia	5 (1)	4 (6)	0.017
Intraabdominal abscess	5 (1)	1 (1)	0.953
Postoperative bleeding	4 (1)	1 (1)	0.796
Wound infection	3 (1)	0 (0)	0.451
Delayed gastric emptying	2 (1)	0 (0)	0.539
Others	9 (3)	2 (2)	0.826
Infectious complication	45 (13)	16 (24)	0.016
Noninfectious complication	21 (6)	6 (9)	0.345
GPS, Glasgow Prognostic Score			

Risk factors of postoperative complication

Table 3 shows the results of the univariate analysis of postoperative complications. The type of the surgical procedure, operative time, blood loss, and GPS were significantly associated with postoperative complications. Table 4 shows the results of the multivariate logistic regression analysis. An operation time ≥ 200 min (hazard ratio [HR] 1.947, 95% confidence interval [CI] 1.080 – 3.512, $p = 0.027$) and a GPS of 1 or 2 (HR 1.877, 95% CI 1.039 – 3.388, $p = 0.037$) were identified as independent risk factors for postoperative complications.

Table 3
Univariate analysis of variables and their potential relation to the occurrence of
postoperative complications

Variables / categories	Patients (n)	Complications n (%)	p-value
Age, years			
<75	306	60 (20)	0.348
≥75	118	28 (24)	
Sex			
Male	282	66 (23)	0.058
Female	142	22 (15)	
Body mass index, kg/m ²			
<25	345	71 (21)	0.853
≥25	79	17 (22)	
Surgical procedure			
Distal gastrectomy	229	36 (16)	0.006
Total gastrectomy	195	52 (27)	
Operation time, min			
<200	179	23 (13)	0.001
≥200	245	65 (27)	
Blood loss, mL			
<250	202	32 (16)	0.017
≥250	222	56 (25)	
Pathological tumor depth			
2 and 3	241	55 (23)	0.228
4	183	33 (18)	
Pathological lymph node metastasis			
(-)	149	33 (22)	0.175
(+)	275	55 (20)	
GPS, Glasgow Prognostic Score			

Variables / categories	Patients (n)	Complications n (%)	p-value
Glasgow Prognostic Score			
0	357	66 (18)	0.008
1 and 2	67	22 (33)	
GPS, Glasgow Prognostic Score			

Table 4. Multivariate analysis of selected variables and their relation to the occurrence of postoperative complications

	OR	95% CI	p-value
Surgical procedure			
Distal gastrectomy			
Total gastrectomy	1.579	0.958–2.601	0.073
Operation time, min			
<200			
≥200	1.947	1.080–3.512	0.027
Blood loss, mL			
<250			
≥250	1.947	1.080–3.512	0.584
GPS			
0			
1 and 2	1.877	1.039–3.388	0.037

OR, odds ratio; CI, confidence interval; GPS, Glasgow Prognostic Score

Discussion

In present study, we investigated the usefulness of the GPS calculated using the serum CRP and serum albumin levels before surgery in predicting postoperative complications in patients with Stage II/III GC who underwent curative surgery. Our results confirm our hypothesis that the preoperative GPS is an independent predictive marker of postoperative complications.

Today, the most commonly used clinical biomarker of systemic inflammation is the serum CRP level. There is an association between systemic inflammation and complications after oncologic surgery [23,

24]. It has been reported that proinflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor- α induce increases in serum CRP levels [25]. Those cytokines produced by various cancers and lymphocytes sensitized to cancer cause systemic inflammatory responses and cancer cachexia [26]. Preoperatively elevated serum CRP levels are associated with an increased incidence of postoperative complications in cancer patients [27]. While, serum albumin is produced in the liver and is the most abundant serum protein [28]. Low albumin is an indicator of malnutrition, and preoperative hypoalbuminemia is often seen in patients with advanced GC. Serum albumin levels decline in patients with poor nutritional status, loss of skeletal muscle, and systemic inflammatory response [29]. In cancer, the progression of the disease is associated with increasing systemic inflammation, leading to hypercatabolism and decreased serum albumin levels [30]. Several studies have demonstrated that hypoalbuminemia increases the incidence of postoperative complications in cancer patients [31–33].

We hypothesized that the GPS could be a useful predictor of postoperative complications in patients with GC because it is calculated based on serum CRP and albumin levels. However, until now, few studies have examined the association between the GPS and postoperative complications. As for previous reports, Fujiwara et al. [34] showed that the GPS was related to blood transfusion requirements and postoperative complications in patients with hepatocellular carcinoma undergoing resection. Moyes et al. [35] reported that a preoperative elevated modified GPS was independently associated with an increased risk of postoperative infectious complications in patients undergoing resection of colorectal cancer. As for the study in patients with GC, Kubota et al. [36] did not find an association between the preoperative GPS and the occurrence of postoperative complications after curative resection of GC. While, in our study, the preoperative GPS was identified a predictor of postoperative complications in patients with GC. The rate of total gastrectomy in the GPS 1 and 2 group in our study was 55%, which was more than twice that in their study. In general, because complications of total gastrectomy, such as anastomotic insufficiency, are higher than those of subtotal gastrectomy, this difference might be explained by the different proportions of total gastrectomy to subtotal gastrectomy in the two studies.

As for possible clinical application of the preoperative GPS, because the preoperative GPS may identify patients with a high risk of postoperative complications, it may assist surgeons in assessing the risk of postoperative complications and choosing an approach that is as safe and minimally invasive as possible. Furthermore, recent studies have shown the efficacy of perioperative immune-nutritional support according to the condition of each cancer patient in reducing the incidence of postoperative complications [37, 38]. In patients with GPS 1, those with low serum albumin and CRP levels may be undernutrition related with cancer. While, those with high serum albumin and CRP levels may be pre-cachexic. Patients of GPS 2 with low serum albumin and high CRP levels may be cancer cachexia. It was reported that supportive nutritional interventions in patients with preoperative cancer cachexia and pre-cachexic may be ineffective, early supportive nutritional interventions for patients with undernutrition related with cancer can be effective for improvement of preoperative nutritional status [37, 38].

Our study had a limitation. our study was retrospective study in a single affiliation. Prospective and multicenter studies in larger cohorts are necessary to clarify the predictive value of preoperative GPS for

postoperative complications in GC patients.

In conclusion, the GPS before surgery may be a useful predictive marker for complications after surgery in patients with stage II/III GC who underwent curative resection. Being aware of the risk of complications after surgery as indicated by the GPS before surgery may promote safe and minimally invasive surgery that we expect will improve outcomes in these patients.

Declarations

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Conflicts of Interest/Competing Interests. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics Approval. This study was approved prior to initiation by the Research Ethics Committee of the Kanagawa Cancer Center (approval number: Epidemiological Study–2019–113).

Consent to Participate. All study participants provided informed consent.

Consent for Publication. All study participants provided consent for publication.

Availability of Data and material. Clinical database consisting of 636 consecutive patients who underwent gastrectomy for advanced GC between January 2003 and June 2014 at Kanagawa Cancer Center was used for this study.

Authors' contributions. Conceptualization and study design were undertaken by Yota Shimoda and Hirohito Fujikawa. Statistical analysis and interpretation were performed by Yota Shimoda. Interpretation of data was performed by all investigators. The article and figures were drafted by Yota Shimoda, Hirohito Fujikawa and Takashi Oshima. Finally, this article was revised and approved by all investigators, and all authors actively participated in this study.

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Figures

Figure 1

Flow diagram of patient selection in this retrospective single-center study of gastric cancer patients. A total of 623 consecutive patients who underwent gastrectomy with D2 lymph node dissection for pStage II/III GC from February 2007 to July 2019 at the Kanagawa Cancer Centre and measured serum albumin and CRP levels before surgery were eligible for this study. Of those patients, patients who underwent preoperative treatment including neoadjuvant chemotherapy, those with remnant GC, those with stage IV disease, and those with non-curative (R1 or R2) resection were excluded. Finally, a total of 424 patients were analyzed.